REMARKS/ARGUMENTS

1. Response to the Rejection of Claims 51 under 35 U.S.C. §112, first paragraph

Claim 51 stands rejected under 35 USC §112, first paragraph. This rejection is respectfully traversed.

Applicant submits herein a Statement on Deposit of Biological Material Pursuant To 37 CFR 1.808, which states that deposit of the biological materials described in the instant application has been made under the terms of the Budapest Treaty, and all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

Therefore, Applicant submit that Claim 51 satisfies the requirement of 35 USC §112, first paragraph.

Accordingly, Applicants respectfully request withdrawal of the rejection based upon 35 U.S.C. §112, first paragraph.

2. Response to the Rejection of Claims 51-67 under under 35 U.S.C. §112, second paragraph

Claims 51-67 stand rejected under 35 USC §112, second paragraph. This rejection is respectfully traversed by the amendment.

The Specification and Claims 51-53 and 61-67 have been amended to comply with 35 U.S.C. §112, second paragraph. Applicants submit that no new matter has been introduced by the amendment.

Accordingly, Applicants respectfully request withdrawal of the rejection based upon 35 U.S.C. §112, second paragraph.

3. Response to the Rejection of Claims 51-67 under under 35 U.S.C. §103(a)

Claims 51-67 stand rejected under 35 USC §103(a) as being unpatentable over Shaw (U.S. Patent No. 4,904,584) in view of the Capon et al. (U.S. Patent No.

5,116,964). This rejection is respectfully traversed.

Applicant submits that nothing in the art of record teaches or suggests the subject matter positively recited in the Claim 51. As recited in Claim 51, Applicant's claimed recombinant polynucleotide that comprises a member selected from the group consisting of (a) a polynucleotide encoding a polypeptide as set forth in SEQ ID NO. 8; and (b) a polynucleotide contained in ATCC® Deposit No: PTA-4607.

The Examiner states that Shaw has only been relied upon for the disclosure of the method of producing recombinant G-CSF using the DNA encoding G-CSF. As pointed out by the Examiner, Shaw fails to teach a polynucleotide encoding both G-CSF and albumin to obtain a fusion protein comprising G-CSF and albumin to increase the half-life of G-CSF.

Shaw's deficiencies are not overcome by Capon et al. Capon et al. fail to teach Applicant's claimed polynucleotide encoding a polypeptide as set forth in SEQ ID NO. 8, or a polynucleotide contained in ATCC® Deposit No: PTA-4607, which encodes a HSA/G-CSF fusion protein.

In reviewing the final Office Action, Applicant has difficulties in understanding the Examiner's construction of Capon et al's teaching. In view of the Examiner's understanding of the prior art of record and the state of art at the time that the present invention was made, Applicant respectfully provides the following remarks.

1. The Examiner states that the teaching of Capon could be taken by any skilled artisan to encompass "any" soluble protein. Applicant respectfully points out that this understanding is an improper construction of the actual teaching of the reference.

Applicant summarizes Capon et al' teaching below:

(1) Capon et al. teach nucleic acid encoding a polypeptide fusion comprising a ligand binding partner protein fused to a stable plasma protein. The ligand binding partner is proteins known to function to bind specifically to target ligand molecules.

(2) Capon et al. teach that the stable plasma protein extends the in vivo plasma half-life of the ligand binding partner when present as a fusion with the ligand binding partner.

(3) Capon et al. specifically teach that a large number of proteins having various structures, sources, and biological functions are excluded from the ligand binding

partner, and therefore, not suitable for their invention. More specifically, Applicant recites below Capon's teaching:

> As used herein, the term "ligand binding partner" specifically excludes polymorphic and nonpolymorphic members of the immunoglobulin gene superfamily, and proteins which are homologous thereto, such as class I and class II major histocompatibility antigens, immunoglobulins, T-cell receptor α, β, γ, and δ chains, CD1, CD2, CD4, CD8, CD28, the γ, δ and ε chains of CD3, OX-2, Thy-1, the intercellular or neural cell adhesion molecules (I-CAM or N-CAM), lymphocyte function associated antigen.3 (LFA.3), neurocytoplasmic protein (NCP-3) poly-Ig receptor myelin-associated glycoprotein (MAG), high affinity IgE receptor, the major glycoprotein of peripheral myelin (Po), platelet derived growth factor receptor, colony stimulating factor.1 receptor, macrophage Fc receptor, Fc gamma receptors and carcinoembryonic antigen (Column 7, lines 35-50, of the reference).

This list excludes more than 20 named proteins and families. Colony stimulating factor 1 receptor is one of these excluded proteins, which is related to G-CSF as discussed in detail in the previous response dated November 21, 2006.

In the section of the reference that the Examiner recited in the Office Action, Capon et al teach "the objects of this invention are accomplished by providing novel polypeptides comprising a ligand binding partner fused to a stable plasma protein". As discussed above, the "ligand binding partner", as defined by Capon, excludes many proteins, more particularly, colony stimulating factor 1 receptor.

Therefore, the Examiner's construction that Capon provides the express motivation to add the albumin to any soluble protein to increase its circulating half-life lacks foundation.

2. The Examiner states that if Capon et al disclosed the instant HSA/G-CSF fusion protein, the rejection would be under 35 USC 102(b), rather than under 35 USC

103(a).

Applicant respectfully points out that Applicant's entire arguments presented in the previous response are based on 35 USC 103(a).

More specifically, *In re Dow Chem.*, 837 F.2d 469, 473, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988) clearly states that "the consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art."

Applicant maintains that because of Capon et al's specific exclusions of the proteins closely related to G-CSF of the instant invention, Capon et al teach away from Applicant's claimed invention.

Therefore, the issue in hand is not whether the prior art has suggested one of ordinary skill in the art to carry out Applicant's claimed invention, rather the fact is that the prior art has particularly excluded the proteins which relates to the subject matter of the instant invention.

As such, it is improper to consider that Capon et al's teaching is the genus, and the instant invention is merely a species of this genus.

3. The Examiner states that vast majority of generic proteins in Class 435 are predicted on the presumption that one can reasonably fuse a first protein to a second protein and expect success. The Examiner further rationalizes that the reason is the vast majority of proteins not requiring a free amino or carboxy group for activity.

Applicant respectfully points out that this is an oversimplification of the daunting tasks that the biopharmaceutical industry is facing. Today, the industry spends millions of dollars every year and hires thousands of Ph.D.s to discover and develop bioactive fusion proteins which are suitable for pharmaceutical use. One of the major difficulties is that after fusion the protein properties can change, which can attribute to many reasons, such as primary, secondary or tertiary structure changes, steric hindrance, interference to binding to the receptors, and etc. Any of these reasons can substantially affect the bioactivity of the fusion proteins. Various scientific publications have reported loss of protein activity, or substantial reduction of the activity after fusion, which diminishes the

utility of the fusion proteins.

Applicant provides below a few research reports that illustrate the practical issues regarding the fusion proteins, and specific findings with regard to G-CSF fusion protein (all references discussed herein are submitted in the enclosed IDS).

(1) Typically, in fusion proteins a peptide linker or spacer is used between two domains to preserve the functions of the individual domains. Argos and Robinson et al have reported that the flexibility and hydrophilicity of the peptide linkers are important for preservation of the functions of the individual domains in a fusion protein (Argos, *J. Mol. Biol.* 211:943-958, 1990 and Robinson et al, *Proc. Natl. Acad. Sci. USA* 95:5929-5934, 1998).

(2) However, Maeda et al have reported that some fusion proteins may lose their activity using the flexible spacer to link the two moieties (Maeda et al, *Anal. Biochem.* 249:147-152, 1997).

(3) Through extensive research of functional domain of human G-CSF, Layton et al have reported that residues 20-46 at the N-terminal and the COOH terminus of G-CSF are involved in binding to G-CSF receptor (Layton et al, *The Journal of Biological Chemistry*, vol. 266, No. 35, Issue of December 15, pp. 23915-23823, 1991). Based on Layton et al's teaching, fusion at either C-terminal or at N-terminal could affect biological activity of the G-CSF domain in the fusion protein, because in the former C-terminus will be blocked; and in the latter residues 20-46 are very close to N-terminus and fusion to another protein at N-terminus could change conformation of adjacent regions.

(4) A practical example of this concern has been reported in Bai et al's most recent research of G-CSF and transferrin fusion protein (Bai et al, *Pharmaceutical Research*, Vol. 23, No. 9, September 2006). In the study of improving the oral efficiency of recombinant G-CSF-Tf fusion protein, Bai et al have found that the G-CSF-Tf fusion protein only retained a small fraction of the in vitro activity of both cell proliferation of G-CSF and TfR-binding of Tf. Bai et al attribute the activity loss of Tf to the modification of the N-terminus of Tf domain rather than a steric hindrance of the receptor biding site in the fusion protein, based on analysis of multiple G-CSF-Tf fusion proteins having different linkers.

In the attempt of reversing the sequence of G-CSF and Tf in the fusion protein, the fusion protein produced from Tf-G-CSF expression was inactive, when assayed by NFS-60 cell proliferation assay (see page 2120, Column 2, the first paragraph, of the reference).

Based on the above, it is apparent that either at the time of the present invention was made, or today, without undue experimentations to actually express a specific fusion protein and testing its property and bio-activity in vitro and in vivo, one of ordinary skill in the art would not be able to predict whether a fusion protein retains the desired biological functions and a reasonable amount of bio-activity that merits its utility.

In the instant situation, Capon et al fail to teach any specifics on how to link albumin to G-SCF, such as through N-terminal or C-terminal, using or not using linkers, what type of linkers, and how to preserve bioactivity of G-CSF.

It is important to understand that the fusion protein encoded by the instant recombinant polynucleotide, as defined in Claim 51, is a directly fused protein that does not have any peptide linker between the two domains. The present inventor has discovered that the rHAS/G-CSF fusion protein encoded by the instant recombinant polynucleotide does not require a peptide linker, and the retained bioactivity of the directly fused protein warrants its utility. This finding is substantially different from the teachings of the existing art.

Therefore, Applicant maintains that Applicant's claimed invention as defined by Claim 51 is not obvious in view of the prior art of record.

With regard to Claims 52-67, these claims are dependent claims of independent Claim 51. Under the principles of 35 U.S.C. §112, 4th paragraph, all of the limitations of each independent claim are recited in its respective dependent claims. As described above, independent Claim 51 is unobvious in view of the prior art of record, as such Claims 52-67 are submitted as being allowable over the art of record.

Accordingly, Applicant respectfully requests withdrawal of the rejection based upon 35 U.S.C. §103(a).

It is respectfully submitted that Claims 51-67, the pending claims, are now in condition for allowance and such action is respectfully requested.

Application No. 10/609,346
Response Dated March 18, 2007
Reply to Office Action of December 19, 2006

Applicant's Agent respectfully requests direct telephone communication from the Examiner with a view toward any further action deemed necessary to place the application in final condition for allowance.

3/18/2007
Date of Signature

By: _____
Yi Li
Registration No. 44,211
Telephone: 305-776-2450

Please address all correspondence to:
Customer Number **27165**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/609,346	Confirmation No.: 1103
Applicant	:	Yu et al	
Filed	:	June 26, 2003	
TC/A.U.	:	1646	
Examiner	:	Prema Maria Mertz	

Old Docket No.: ZYU-0603
New Docket No.: 118.01
Customer No.: 27165

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT ON DEPOSIT OF BIOLOGICAL MATERIAL PURSUANT TO 37 CFR 1.808

Sir:

Applicant submits that the deposit of the biological materials described in the patent application Serial No. 10/609,346 has been made under the terms of the Budapest Treaty on the International Recognition of the Deposit of the Microorganisms for the Purpose of Patent Procedure at ATCC® on August 21, 2002. This deposit has received the Patent Deposit Designation No. PTA-4607.

Applicant submits herein a copy of the Certificate received from ATCC® dated September 20, 2002.

CERTIFICATE OF TRANSMISSION

I hereby certify that, on the date shown below, this correspondence is being facsimile transmitted to the Commissioner of Patents, at Fax No. (571) 273-8300.

YI LI
Typed or printed name of person signing this certificate

Signature _____ Date 3/18/2007

Applicant states that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

Therefore, Applicant respectfully submits that ATCC® PTA-4607 deposit is in full compliance with 37 CFR 1.803-1.809, and it satisfies the requirement of 35 USC §112, first paragraph.

3/18/2007
Date of Signature

By: _____
Yi Li
Registration No. 44,211
Agent of Record

Please address all correspondence to:

Customer Number **27165**

ATCC

10801 University Blvd • Manassas, VA 20110-2209 • Telephone: 703-365-2700 • FAX: 703-365-2745

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3 AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

FortuneRock Inc,
Attn: Dr. Zailin Yu
30306 Meridien Circle
Union City, CA 94587

Deposited on Behalf of: FortuneRock, Inc.

Identification Reference by Depositor:	**Patent Deposit Designation**
Consotium of Yeast, mixture of four strains of Pichia pastoris {ZY-HSA/hIL-11:ZY-HSA/hEPO:ZY-HSA/hG-CSF:ZY-HSA/hGM-CSF}: ZY-HSA/CPSFs (Ref. Docket or Case No.: ZYU-0602)	PTA-4607

The deposit was accompanied by: __ a scientific description __ a proposed taxonomic description indicated above.

The deposit was received August 21, 2002 **by this International Depository Authority and has been accepted.**

AT YOUR REQUEST: X **We will inform you of requests for the strain for 30 years.**

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested September 9, 2002. **On that date, the culture was viable.**

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Marie Harris

Marie Harris, Patent Specialist, ATCC Patent Depository **Date:** September 20, 2002